The Gerbich blood group system: a review

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Antigens in the Gerbich blood group system are expressed on glycophorin C (GPC) and glycophorin D (GPD), which are both encoded by a single gene, *GYPC*. The *GYPC* gene is located on the long arm of chromosome 2, and Gerbich antigens are inherited as autosomal dominant traits. There are 11 antigens in the Gerbich blood group system, six of high prevalence (Ge2, Ge3, Ge4, GEPL [Ge10*], GEAT [Ge11*], GETI [Ge12*]) and five of low prevalence (Wb [Ge5], Ls^a [Ge6], An^a [Ge7], Dh^a [Ge8], GEIS [Ge9]). GPC and GPD interact with protein 4.1R, contributing stability to the RBC membrane. Reduced levels of GPC and GPD are associated with hereditary elliptocytosis, and Gerbich antigens act as receptors for the malarial parasite *Plasmodium falciparum*. Anti-Ge2 and anti-Ge3 have caused hemolytic transfusion reactions, and anti-Ge3 has produced hemolytic disease of the fetus and newborn (HDFN). ***Immunohematology* 2010;26:60–65.**

Key Words: blood group, Gerbich, glycophorin, GPC

History

In 1960, Rosenfield et al.[1] described the first examples of anti-Gerbich in the sera of three women, including Mrs. Gerbich, after whom the blood group system is named. A year later, Cleghorn[2] and Barnes and Lewis[3] reported on a Turkish Cypriot woman, Mrs. Yus, whose RBCs were compatible with two of the original three sera but were incompatible with serum from Mrs. Gerbich. In 1970, Booth et al.[4] reported on the prevalence of the Gerbich (GE) blood group in Melanesians, and in 1972, Booth[5] reported that certain Ge+ individuals demonstrated an antibody that was compatible with RBCs expressing the Gerbich or the Yus phenotype, but was incompatible with up to 15 percent of Ge+ Melanesians.

After Zelinski et al.[6] demonstrated that Gerbich is genetically discrete from all other existing systems, the Gerbich antigen collection (ISBT Collection 201) was upgraded to the GE blood group system (ISBT system symbol GE and number 020) by the ISBT Working Party on Terminology for Red Cell Surface Antigens.[7]

Biochemistry

In 1984, Anstee et al.[8] reported that individuals who lack Gerbich blood group antigens have alterations in their erythrocyte membrane sialoglycoproteins. In 1984, these proteins were called β-syaloglycoprotein and γ-syaloglycoprotein; however, the current terminology is glycophorin C (GPC) and glycophorin D (GPD). Gerbich antigens are found on GPC and GPD. These sialic acid–rich glycoproteins are also known as CD236R, and they attach to the RBC membrane through an interaction with protein 4.1R and p55. GPC and GPD contain three domains: an extracellular NH_2 domain, a transmembrane domain, and an intracellular or cytoplasmic COOH domain (Figure 1). GPC and GPD are encoded by the same gene, *GYPC*. When the first AUG initiation codon is used, GPC is encoded, whereas when the second AUG is used, GPD is encoded. Thus, GPD is a shorter version of GPC, and the amino acids in GPD are identical to those found in GPC but lacking the first 21 amino acids at the N-terminal of GPC.[9,10]

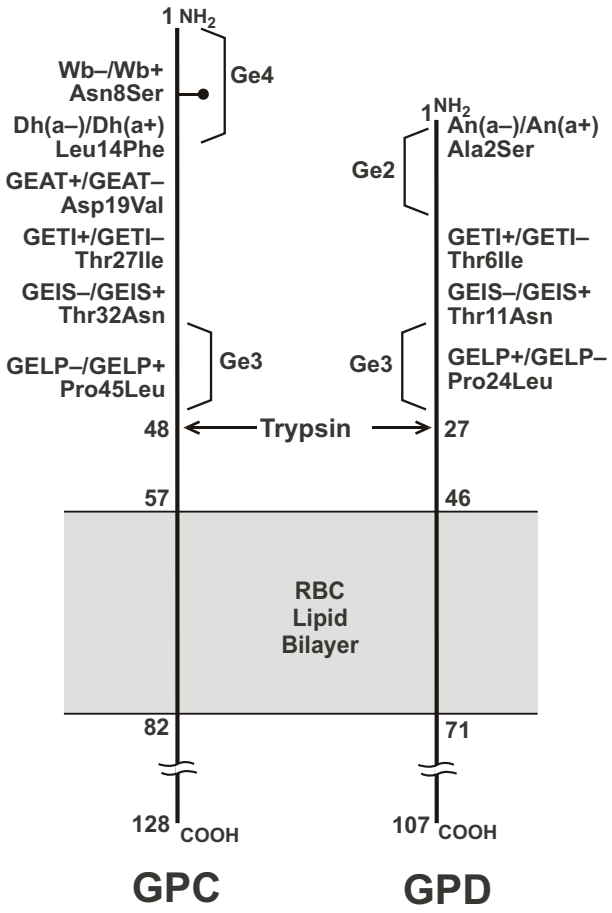

Fig. 1. Molecules (glycophorin C [GPC] and glycophorin D [GPD]) showing location of various Gerbich antigens. The stick figures give the amino acid residue numbers defining the extracellular, transmembrane, and intracellular domains of GPC and GPD. Also shown is the trypsin cleavage site and location of all antigens except Ls^a, which is the result of amino acids encoded by the duplication of exon 3.

*Nomenclature pending approval by the ISBT Working Party on Terminology for Red Cell Surface Antigens.

Certain Gerbich antigens (Ge4, Wb, Dh[a], GEAT) are only expressed on GPC, two (Ge2, An[a]) are only expressed on GPD, and others (Ge3, Ls[a], GEIS, GEPL, GETI) are expressed on both GPC and GPD. Despite the fact that GPC possesses all of the amino acids that are found on GPD, the likely explanation for why some antibodies only react with GPD is that the antibodies require a conformational epitope that is present at the amino terminus of GPD but absent in the subterminal amino acid sequence of GPC. Some examples of anti-Ge2 do not react with RBCs after the acetylation of membrane proteins with acetic anhydride, suggesting that a free amino group is involved in the epitope detected by these antibodies.[11] A diagram showing the trypsin cleavage site and location of Ge2, Ge3, and Ge4 antigens is given in Figure 1.

In 1990, Reid et al.[12] reported that GPC plays a functionally important role in maintaining erythrocyte shape and regulating the membrane properties through its interaction with protein 4.1R. In 1993, Alloisio et al.[13] showed that p55, a peripheral membrane protein in human erythrocytes, is associated in precise proportions with the protein 4.1R–GPC complex, linking the cytoskeleton and the membrane. The absence of GPC and GPD is associated with hereditary elliptocytosis, which is described later in this discussion.

Inheritance and Molecular Genetics

In 1986, Colin et al.[14] cloned the gene *GYPC*, and Mattei et al.[15] determined that *GYPC* is located on chromosome 2, in the region of q14–q21. The *GYPC* gene consists of 13.5 kilobase pairs (kbp) of gDNA, comprising four exons. Exons 2 and 3 are homologous, with less than 5 percent nucleotide divergence. This can lead to unequal crossing over during meiosis and loss (outsplicing) of exon 2 or exon 3. In 1987 Le Van Kim et al.[16] reported that a deletion of approximately 3 kb in the *GYPC* gene is associated with the Gerbich blood group deficiency types Yus (GE:–2,3) and Gerbich (GE:–2,–3). In 1989, High et al.[17] reported that the absence of exon 2 results in the Yus phenotype, whereas the absence of exon 3 results in the Gerbich phenotype. The Gerbich phenotype has also been produced by a nucleotide change and deletion of exon 3 of the *GYPC*.[18] The Leach phenotype (GE:–2,–3,–4) may be produced by two different mechanisms. The "PL" type of the Leach phenotype is caused by a deletion of exons 3 and 4, whereas the "LN" type is a consequence of a 131G>T nucleotide change (134delC in exon 3; Trp44Leu) that leads to a frame shift and a premature stop codon. Other Ge antigens are a consequence of nucleotide changes in *GYPC* (Table 1).[19] The products of the Ge alleles are inherited in an autosomal codominant manner.[20] A gene map is shown in Figure 2.

Table 1. Summary of nucleotide and amino acid changes in Ge phenotypes

Phenotype	Traditional name	Nucleotide change exon/ intron	Amino acid change	Ethnicity (occurrence)
GE:–2,3,4	Yus type	del exon 2	Deletion of amino acids, altered GPC	Hispanic, Israeli, and Mediterranean populations (rare)
GE:–2,–3,4	Gerbich type	del exon 3	Deletion of amino acids, altered GPC	Melanesians (50%) Others (rare)
GE:5	Wb+	23A>G in exon 1	Asn8Ser in GPC	Wales and Australia (few) Others (rare)
GE:6	Ls(a+)	Duplicated or triplicated exon 3	Duplication, altered GPC	Blacks (2%) Finns (1.6%) Others (Rare)
GE:7	An(a+)	67G>T in exon 2	Ala23Ser in GPC^; Ala2Ser in GPD	Finns (0.2%) Others (rare)
GE:8	Dh(a+)	40C>T in exon 1	Leu14Phe in GPC	Original proband was Danish (rare)
GE:9	GEIS+	95C>A in exon 2	Thr32Asn in GPC; Thr11Asn in GPD	Japanese (rare)
GE:–10	GEPL–	134C>T in exon 3	Pro45Leu in GPC[19] Pro24Leu in GPD	(rare)
GE:–11	GEAT–	56A>T in exon 2	Asp19Val in GPC[19]	(rare)
GE:–12	GETI–	80C>T in exon 2	Thr27Ile in GPC[19] Thr6Ile in GPD	(rare)
Null phenotype				
GE:–2, –3,–4	Leach type (PL)	del exons 3 and 4		(rare)
GE:–2, –3,–4	Leach type (LN)	131G>T; 134delC in exon 3	Trp44Leu; 45fs; 55Stop	(rare)

GPC = glycophorin C; GPD = glycophorin D.
^ the altered GPC does not express An[a].

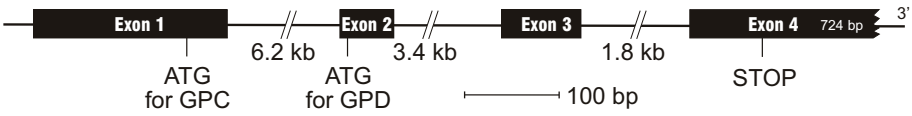

Fig. 2. Glycophorin C (*GYPC*) gene map. *GYPC* is composed of four exons and three introns that are distributed over 13.5 kb of genomic DNA. Exons are the regions of the gene sequence that code for the amino acids that constitute the glycoproteins, GPC and GPD. The introns separate the exons, and they are not encoded. Locations of the ATG (start codon) for initiation of GPC and GPD are indicated.

Gerbich Antigens

There are six high-prevalence antigens and five low-prevalence antigens in the Gerbich blood group system. As examples of anti-Ge1 are no longer available, the Ge1 antigen was declared to be obsolete by the ISBT working party for terminology of red cell surface antigens.

High-Prevalence Antigens

Ge2 is absent from RBCs with the Yus, Gerbich, or Leach phenotype. Ge2 is located at the NH_2 terminal 19 amino acids of GPD and is not expressed on GPC. Ge3 is absent from RBCs with the Gerbich or Leach phenotype. Ge3 is expressed on both GPC and GPD within their extracellular portion close to the lipid bilayer. Ge4 is absent only from RBCs with the Leach phenotype, which is the null phenotype in the Gerbich blood group system. Ge4 is located within the NH_2 terminal 19 amino acids of GPC (Figure 1; Table 2).

The Ge-negative phenotypes, which can be difficult to differentiate by hemagglutination with polyclonal antibodies, are readily distinguished by testing trypsin-treated RBCs with monoclonal anti-Ge4. The reaction patterns are shown in Table 3.

Three other high-prevalence Ge antigens, GEPL (Ge10*), GEAT (Ge11*), and GETI (Ge12*), are each a consequence of a nucleotide change in *GYPC* (Table 1).[19]

Table 2. Gerbich-negative phenotypes

Traditional phenotype name	ISBT phenotype name	Antibodies	Compatible with
Yus	GE:–2,3,4	Anti-Ge2	GE:–2,3,4, GE:–2–3,4, and GE:–2,–3,–4
Gerbich	GE:–2,–3,4	Anti-Ge3 or anti-Ge2	GE:–2,–3,4 and GE:–2,–3,–4 (if anti-Ge2 then compatible with GE:–2,3,4)
Leach	GE:–2,–3,–4	Anti-Ge4, anti-Ge3, or anti-Ge2	GE:–2,–3,–4 only

Table 3. Differentiation of Ge-negative phenotypes using monoclonal anti-Ge4

RBCs	Normal	Yus	Gerbich	Leach
Untreated	4+	0–2+	0–2+	0
Trypsin-treated	0	0	4+	0

Low-Prevalence Antigens

Wb (Ge5)(Webb),[21] An^a (Ge7)(Ahonen),[11] Dh^a (Ge8)(Duch),[22] and GEIS (Ge9)[23] each result from a nucleotide change in *GYPC* (Table 1). The Wb (Ge5) antigen results from the substitution Asn8Ser near the NH_2 terminus of GPC. This substitution interrupts the consensus sequence for *N*-glycosylation (Asn-X-Ser/Thr), which results in a loss of the *N*-glycan and the gain of an *O*-glycan.[24] Ls^a (Ge6)(Lewis)[25] results from a novel amino sequence encoded by a duplication or triplication of exon 3 of *GYPC*. The allele with a duplication of exon 3 is the reciprocal product of the altered *GYPC* (*GYPC.Ge*) that lacks exon 3 and encodes the Gerbich phenotype.

Altered Antigen Expression

In protein 4.1R–deficient RBCs, Gerbich antigens are expressed weakly. As GPC and GPD interact with protein 4.1R, an absence of this protein causes a reduced level of GPC and GPD in the RBC membrane.[12] The weakening of Ge2 and Ge3 antigens can be such that, under certain testing conditions, they can appear to be absent.

Gerbich-negative RBCs may show a weakened expression of certain other blood group antigens, notably Kell and Vel. Nine of 11 GE:–2,–3 samples showed different degrees of weakening of Kell system antigens, whereas none of six GE:–2,3 samples showed Kell depression.[26] Similarly, 3 of 14 examples of anti-Vel failed to react with four GE:–2,–3,4 samples, but they did react with one example each of GE:–2,3,4 and GE:–2,–3,–4 RBC samples.[27]

Antibodies to Gerbich Antigens

Anti-Ge2

Anti-Ge2 may be immune or naturally occurring and reacts with an antigen on GPD. Anti-Ge2 is usually an IgG antibody that reacts by the IAT. Some examples of anti-Ge2 have been complement binding and hemolytic. Treatment of RBCs with papain or ficin results in the loss of reactivity with anti-Ge2; however, when RBCs treated with 200 mM DTT are tested with anti-Ge2, variable results are obtained. Individuals with Yus, Gerbich, or Leach phenotypes can make anti-Ge2 (Table 2).[28] The clinical significance of anti-Ge2 is discussed below.

Anti-Ge3

Anti-Ge3 reacts with an antigen on both GPC and GPD. Anti-Ge3 is usually an IgG antibody that reacts by the IAT; however, some IgM forms have been reported. Many examples of anti-Ge3 bind complement and are hemolytic. Anti-Ge3 reacts with RBCs that were treated with papain or ficin and 200 mM DTT. Individuals with Gerbich or Leach phenotypes can make anti-Ge3 (Table 2).[28] The clinical significance of anti-Ge3 is discussed later.

Anti-Ge4

Alloanti-Ge4 is very rare; only one human example has been described That antibody was IgG, and it reacted by the IAT.[29] Numerous examples of monoclonal antibodies with Ge4 specificity have been produced.[30,31] Treatment of RBCs with papain or ficin results in the loss of reactivity with anti-Ge4, however, treatment of RBCs with 200 mM DTT does not affect their reactivity with anti-Ge4.[28] Individuals with Leach phenotype can make anti-Ge4 (Table 2).[28] There is no information about the clinical significance of anti-Ge4.

Antibodies to Low-Prevalence Antigens
Wb(Ge5), Ls^a(Ge6), An^a(Ge7), Dh^a(Ge8), GEIS (Ge9)

These antibodies may be IgM or IgG, and they may be naturally occurring. They react at room temperature and by the IAT, and none are complement-binding. Treatment of antigen-positive RBCs with papain or ficin results in the loss of reactivity with these antibodies; however, the antigens are resistant to treatment with 200 mM DTT.[28] There are no reports of clinically significant transfusion reactions or HDFN associated with these antibodies.

Clinical Significance
Transfusion Reactions

Some examples of anti-Ge2 and anti-Ge3 have caused moderate transfusion reactions—both immediate and delayed; however, other examples have failed to produce shortened RBC survival when antigen-positive incompatible units were transfused.[32–34] Pearson et al.[35] reported a case of alloanti-Ge in which there were discrepant results between an in vivo chromium-51 (^{51}Cr) survival study and an in vitro monocyte assay. In that case, the in vivo ^{51}Cr survival study yielded zero survival of Gerbich-positive cells after 24 hours; however, a monocyte assay showed less than 1 percent lysis of Gerbich-positive cells. The clinical significance in this case was not determined because only Gerbich-negative blood was transfused during surgery.

HDFN

Anti-Ge2 has been associated with a positive DAT in infants with GE:2 RBCs; however, no cases of clinical HDFN have been reported. By contrast, anti-Ge3 appears to be capable of causing severe HDFN. An interesting recent publication shows that the mechanism for anemia, and possibly for thrombocytopenia, in HDFN caused by anti-Ge3 may be attributed to interference with the erythropoietin signaling cascade.[36] Similar to the mechanism of erythroid suppression described in HDFN caused by anti-K,[37] anti-Ge3 has been associated with antibody-dependent hemolysis, as well as inhibition of erythroid progenitor cell growth in the infant. In these cases, the affected infants may require initial treatment at delivery, followed by monitoring for signs of anemia for several weeks after birth.[38,39]

Autoimmune Hemolytic Anemia

Several cases of autoimmune hemolytic anemia (AIHA) with anti-Ge specificity have been reported. In two cases, the course of the AIHA was as expected, i.e., the patients typed Ge+, their serum demonstrated anti-Ge antibodies, their DATs were positive, and eluates from the autologous RBCs demonstrated Ge-like antibodies.[40,41]

In one case, the patient typed Ge+ and the serum was nonreactive, but an eluate from the patient's RBCs demonstrated anti-Ge specificity.[42] This is the first report of IgM-mediated warm AIHA associated with autoanti-Ge. In two other cases, the patients typed Ge+ and their serum demonstrated anti-Ge, but their serum failed to react with the autologous RBCs (DAT-negative).[43,44] However, in both of these cases, eluates from the patients' RBCs demonstrated an antibody with Ge specificity. Without the eluate results, these cases could have been confused with alloanti-Ge. One possible explanation for these findings could be a weakening of the Gerbich antigens during the course of the AIHA. In cases of severe life-threatening hemolysis, it might be advisable to select Ge-negative units for transfusion.

Hereditary Elliptocytosis

Gerbich antigens interact with protein 4.1R, which contributes to the stability of the RBC membrane.[12,45,46] In 1986, Daniels et al.[31] described a family with hereditary elliptocytosis that was associated with the Leach phenotype. In 1991, Telen et al.[47] further explained the molecular basis for the elliptocytosis as the deficiency of GPC and GPD that is associated with the Leach phenotype. Patients with hereditary elliptocytosis rarely require transfusions. If such a patient requires transfusions for other reasons (e.g., surgery) and the patient demonstrates alloanti-Ge, it might be prudent to select Gerbich-negative units for transfusion, if such rare blood is available.

Malaria

In northern Papua New Guinea, where malaria is endemic, Serjeantson[48] reported in 1989 that Gerbich-negative Melanesians appear to have a selective advantage for avoiding infections with *Plasmodium falciparum* and *Plasmodium vivax*. Subsequent studies confirmed that *P. falciparum* binds to RBCs through a receptor on wild-type GPC, which is missing on Gerbich-negative cells that express a truncated form of GPC.[49–51]

Summary

The Gerbich blood group system is composed of six high-prevalence antigens, which are expressed on GPC, GPD, or both. GPC and GPD are encoded by a single gene, *GYPC*, which is located on the long arm of chromosome 2. By interacting with protein 4.1R, GPC and GPD contribute stability to the RBC membrane, and a deficiency in these proteins has been associated with hereditary elliptocytosis. Also, Gerbich antigens apparently act as receptors for *P. falciparum malaria*. Certain Gerbich antibodies are clinically significant, e.g., anti-Ge2 and anti-Ge3 have caused hemolytic transfusion reactions, and anti-Ge3 has produced HDFN.

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